(page 13, lines 5-19). At page 14, Applicants discuss one of the reasons behind the development of their invention.

> "Thus, if useful amounts of the non-steroidal anti-inflammatory drugs could be delivered to a site in need thereof without carriage of substantial amounts away from the site to be treated, then the use of a non-steroidal anti-inflammatory drug may have many other useful applications." (page 14, lines 10-14)

Applicants thereafter, in the Application, discuss their Invention particularly having discovered the topically applied quick penetrating (best-targeting the epidermis) and subsequently remaining there for a prolonged period of time, dosage amounts taken from compositions which comprise a therapeutically effective amount of a drug for example, NSAID and an amount of a form of hyaluronic acid as discussed in the Application. Applicants have found the invention particularly useful for treating specific diseases such as basal cell carcinoma, actinic keratoses lesions, and other diseases and conditions of the skin as discussed at page 15, lines 3 to 12 and to the treatment of pain (page 23, lines 4-5). Applicants state that the use of these formulations provide a systemic independent effect. Applicants teach that a drug which inhibits prostaglandin synthesis may be used such as a non-steroidal anti-inflammatory drug (page 16, lines 6-7). At page 16, Applicants discuss at line 18:

> "This blockage of prostaglandin synthesis then unblocks the macrophages and permits the macrophages of the patient proximate the lesion (for example, the basal cell carcinoma) to destroy the lesion or condition."

At page 18, lines 10-12 teach the person skilled in the art to use the formulation "a number of times daily (for example, 3 times daily for a period of time, for example, 2 to 4 weeks to clear the lesion."

Applicants, at page 18, refer to two formulations which can be used. The first between lines 13 and 17 comprises 3% diclofenac and 2 $^1/_2$% hyaluronic acid (sodium hyaluronate - molecular weight 661,600) in a gel formulation, with the excipients being glycerine (5%), benzyl alcohol (3%), (acting in part as a solubilizer and preservative), and sterile water, the balance. Another formulation, at page 18 between lines 18 and 22 comprise 3% diclofenac and $2^1/_2$% hyaluronic acid (sodium hyaluronate - molecular weight 679,000) gel formulation with excipients being benzyl alcohol (1%) (a preservative), methoxypolyethylene, glycol 350 (20%) (a soubilizer), and sterile water (the balance). At page 19, the lotion containing hyaluronic acid and drug may be a 1% lotion of hyaluronic acid.

Directions are thereafter provided to persons skilled in the art to use the invention,

> "While the above formulations are suggested, provided these is sufficient hyaluronic acid (for example, sodium hyaluronate) to facilitate the penetration to the site in the skin (for example, epidermis) fo a sufficient amount of a drug which inhibits prostaglandin synthesis, preferably an NSAID (for example, diclofenac), to block prostaglandin synthesis, then the formualtions may be of any suitable

form, for example, a 1% lotion of hyaluronic acid, or cream or any suitable combination.

While higher molecular weights of the hyaluronic acid and forms thereof may be used and may penetrate more rapidly, where the molecular weight of the hyaluronic acid chosen for use is very large, there may not be as much penetration. Thus, the hyaluronic acid may be autoclaved, to break down the hyaluronic acid to fragments of lesser molecular weight. Furthermore, because there is little concern with respect to the toxicity or adverse effects with the use of, for example, the NSAIDS with the hyaluronic acid, after solubilizing the NSAID in a suitable solubilizer, the NSAID may be combined as needed."

At page 19, between lines 4 and 12, Applicants discuss the molecular weights of hyaluronic acid that may be used. These discussions must be combined with the above when the choice of the hyaluronic acid to be used has a molecular weight which is very large and may not provide sufficient penetration. The hyaluronic acid may therefore, be autoclaved to break down the hyaluronic acid to fragments of lesser molecular weight.

As indicated, because there is little concern with respect to toxicity or adverse effects of the use of for example, the NSAIDS with the hyaluronic acid after solubilizing the NSAID in a suitable solubilizer, the NSAID may be combined as needed. Thus, persons skilled in the art are taught that they can adjust the amount of the NSAID upwards as required (an excess to a usual dosage amount). The Examiner is asked to note as this Application is a Continuation-

In-Part Application of Application Serial No. 07/675,908 which is incorporated by reference, the discussion at (i) page 25, line 17 to page 26, line 14, (ii) page 26, lines 32-37 and page 23, line 36 to page 24, line 6 with respect to effective transport and toxicity. A copy of the PCT Application (International Application No. PCT/CA90/00306, International Publication No. WO91/04058) from which Application 07/675,908 entered the National Phase in the United States is attached as **Schedule "AA"**.

At page 21 of **Schedule "AA"** between lines 9 to 16, there is a discussion of the transportation of the chemical to the site in a tumour by the use of hyaluronic acid and thus, the penetration of the hyaluronic acid. At page 22, lines 20 to 25, Applicants discuss the reduction in the major toxic side-effects such as gastro-intestinal distress, neurological abnormalities, depression, etc., "even at elevated amounts of indomethacin (if necessary)".

Beginning at page 22 to page 23, line 5, this Application provides that the penetration with the NSAIDS and hyaluronic acid provide dramatic relief of pain immediately in the patient. A mechanism for the operation of the formulations is discussed at page 23, line 21 to page 24, line 14 (to which Applicants should not be limited). As stated, Applicants postulate when the formulation is administered topically for example, to treat a disease or condition (for example, basal cell carcinoma or actinic keratoses), "the hyaluronic acid passes between the cells (in the stratum corneum, epidermis, and dermis) to the areas deficient in hyaluronic acid (or forms thereof), taking, drawing, carrying or pulling the NSAID with it to the sites of prostaglandin synthesis, penetrating to inhibit prostaglandin synthesis. The NSAID now being proximate the Paccinian nerve bundle (superficial nerve bundles at the end of the nerves) gives pain relief. The macrophages (which have been blocked) are then unblocked and act to destroy the disease or condition. . ." Furthermore, the formulation slowly

passes through the skin staying longer in the skin at the site. Therefore, after having an immediate effect (for example, relieving pain and acting on the basal cell carcinoma, actinic keratoses, and other disease or condition), the NSAID-hyaluronic acid combination remains longer at the site in need of treatment before it is cleared, Applicants believe, through the lymphatic system. Please note, at page 24, lines 20-26 the statement that 15 minutes after the application of one of Applicants' formulations, about three times the amount of Applicants' formulation has penetrated into the skin (particularly the epidermis) than formulations and combinations not containing hyaluronic acid but containing the same drug.

Beginning at page 28, examples are given. These examples include formulations which contain NSAIDS and forms of hyaluronic acid. The formulation beginning at page 28, line 15 noted as "Our Formulation", EPDICL01 contained 1% diclofenac and 3% "HA" gel. "HA" in this case is sodium hyaluronate with a molecular weight of 661,600 daltons. "Our Formulation" is compared to the "Voltarol" + Emulgel and a 1% diclofenac gel control referred to at page 29. The samples applied to a quantity of skin having an exposed skin surface of 9.6 cm^2 with a total amount of gel being applied as 192 mg. (see page 30, lines 11 to 17) so that 20mg./cm^2 of the formulation is applied evenly over the surface of the skin (page 31, lines 2 to 3). The results are shown at page 32. It is noted that most of formulation EPDICL01 is in the top portion of the skin (the epidermis) whereas the other formulations do not contain the same amounts (per gram of skin). (See Figures 1, 2, and 3 of the Application.) Thus, it is clear that Applicants' formulation does not drive the medicine through the skin into the blood for treatment of the disease or condition in the area (not a systemic action) (see page 33, lines 7 to 9) but, rather transport the medicine to the epidermis where it is required for the treatment of the disease and/or pain.

Between pages 34 and 43 inclusive, nine (9) Formulations and their manufacture are discussed containing various percentages of various NSAIDS and various percentages of sodium hyaluronate. The Examiner will note the following percentages of NSAIDS and forms of hyaluronic acid in the formulations asserted useful to treat the diseases and conditions as follows:

	Percentage by Weight of Formulation
Formulation 1	
Diclofenac Sodium	3%
Sodium Hyaluronate	2.5%
Formulation 2	
Diclofenac Sodium	3%
Sodium Hyaluronate	2.5%
Formulation 3	
Diclofenac Sodium	3%
Sodium Hyaluronate	2.5%
Formulation 4	
Ibuprofen	5%
Sodium Hyaluronate	3%
Formulation 5	
Piroxicam	2%
Sodium Hyaluronate	2.5%
Formulation 6	
Ibuprofen	5%
Sodium Hyaluronate	1.5%
Formulation 7	
Diclofenac	1%
Sodium Hyaluronate	3%
Formulation 8	
Diclofenac Sodium	1%

Sodium Hyaluronate	3%

Formulation 9

Ibuprofen	5%
Sodium Hyaluronate	1.5%

It is therefore clear from the Disclosure that the amounts of sodium hyaluronate in formulations actually identified in the Application have a range of the form of sodium hyaluronate between 1% (see page 19, line 1) and 3% by weight of the composition and the amount of the NSAID in the composition is between 1% and 5% of the composition and thus also of the dosages taken from the composition. These compositions made are all multigram compositions put in containers from which the dosages used can be taken.

Specifications for forms of hyaluronic acid are provided between at page 43, line 34 to page 49, line 15 which must be read in conjunction with that part found at page 19, lines 3 to 12. Persons skilled in reading this portion will appreciate how the molecular weights of the forms of hyaluronic acid used are determined. Persons skilled in the art need only contact the Manufacturer to determine molecular weight. No experimentation at all would be required.

To determine blood levels in patients using different formulations, Applicants compared the use of Voltarol Emulgel with a diclofenac preparation in hyaluronic acid (page 49, lines 21-23). Two grams of each formulation was applied three times daily. The formulation, from reviewing the formulations in the Application, would contain an amount between 2.5% and 3% sodium hyaluronate. At page 51, blood levels were also determined having regard to using Proflex (a formulation containing Ibuprofen) and a formulation containing hyaluronic acid and Ibuprofen which comprised 1.5% sodium hyaluronate having a molecular weight of 207,000 and Ibuprofen having a percentage of 5%.

The results indicate there is far less in the blood using hyaluronic acid to administer the NSAID (page 52, line 51).

Thus, of the 2 grams administered referred to at page 50, line 7 in the Application, the lowest percentage of hyaluronic acid is 1.5%. 1.5% of two grams is 30mg. Thus, the amounts of the form of hyaluronic acid used in this Example can range from 30 to 60 mg. of HA in the two gram samples and are absolute amounts administered to the calves.

Thus, having regard to the tests only and no other discussion in the Application, it is clear that 20 mg/cm^2 is applied of a gel (discussed at page 30 to 31) comprising 3% hyaluronic acid and a discussion of blood levels from the test results discussed at page 49 to 52 inclusive involve amounts of 30-60mg. of sodium hyaluronate which is the pharmaceutically acceptable tolerable salt of hyaluronic acid.

Thereafter, specific examples are provided of patients who were treated with Applicants' formulation. The patient in Example 1 (basal cell carcinoma) is treated with Formulation 1. The patient in Example 2 (basal cell carcinoma) is treated with Formulation 2. The patient in Example 3 (basal cell carcinoma) is treated with Formulation 2. The patient in Example 4 (actinic keratoses) is treated with Formulation 1. The patient in Example 5 is treated for pain in the back. The patient in Example 6 (basal cell carcinoma), it can be inferred, is treated with one of the formulations comprising diclofenac sodium with sodium hyaluronate and excipients. The patient in Example 7 is treated with methotrexate in hyaluronic acid for the treatment of psoriasis. Example 8 is treated for dermal (skin) metastases in a fibratic scar form and metastatic cancer in the form of musculo-skeletal involvement in her thorax with diclofenac and

hyaluronic acid such that her pain decreased dramatically and her skin and boney involvements steadily improved.

Applicants have taken the liberty of carefully reviewing the application and the teachings thereof herein to assist the Examiner with respect to the amendments to the Claims now included in the Application and the amendments thereto as required by the Examiner. Applicants have pointed to the basis for the range of amounts and percentages of the forms of hyaluronic acid, and the percentage range for the amounts of the NSAID and other medicines referred to (even excess amounts which can be tolerated). Applicants have referred to the diseases treated and the amounts given with respects to tests undertaken to show penetration and passage through the skin.

In view of the above submissions, Applicants respectfully submits that the Claims as now presented are fully supported by the Disclosure. Persons skilled in the art reading the Application and its contents in Applicants' respectful submissions would use the exemplary amounts taught in the Application (why else have they been provided?). Patients applying the dosages from the formulations would take some out and apply to the site of for example, the basal cell carcinoma. The squeezed out portions will work. The concentrations will work. This is shown in the test results. The specification is therefore, in Applicants' respectful submission, enabling for the use of the dosages. No undue experimentation would be required. People respond differently and some would require more applications and others less. However, over time, it is clear the patients and doctors will see differences with the basal cell carcinoma.

The Examiner also takes the position that the specification fails to present the dosages for treating basal cell carcinoma and that undue

experimentation would be required. Applicants repeat the above. Persons skilled in the art would direct persons to take out amounts from the formulation as discussed above and which they know would work. Because penetration is established (blood level tests), persons skilled in the art would know from this alone, the dosages would work.

Applicants have previously made substantial submissions with respect to the requirements of a patent application to substantiate the utility of a formulation where the formulation is used for treating a disease. Applicants adopt its previous submissions. In addition thereto, Applicants submit that the Application is addressed to persons skilled in the art and persons skilled in the art would appreciate that the formulations provided in Applicants' Application in view of the test results, substantiate the treatment of all the diseases and conditions for which the formulations are asserted to be useful (including basal cell carcinoma). Persons reading the Application would know that the results indicate that Applicants formulations and methods of treatment and dosage compositions used for those methods of treatment can be used successfully to treat and resolve, among other diseases and conditions discussed in the Application, basal cell carcinoma, actinic keratoses, psoriasis, treat pain topically, and treat a patient with dermal (skin) metastases in a fibratic scar form and metastatic cancer in the form of musculoskeletal involvement in the thorax by topical application. (See Example 8 at page 56.) The molecular weights of the forms of hyaluronic acid useful for the invention have been disclosed. No undue experimentation would be required as asserted by the Examiner.

Although at one time the Patent Office required at least one "working" example as part of the disclosure of the specification, there is no absolute statutory requirement for such an example if the disclosure is such that one skilled in the art can practise the claimed invention. In re Bordowski et al.

(CCPA 1970) 422 F2d 904, 164 USPQ 642; Ex parte Nardi et al. (BPAI 1986) 229 USPQ 79. Use of "prophetic" examples does not automatically make a patent non-enabling merely because there can be no guarantee that the examples would actually work. Atlas Powder Co. v. E.I. DuPont de Nemours & Co. (CAFC 1984) 750 F2d 1569, 224 USPQ 409.

Although a specification preferably should contain a "working" example to ensure that the "how to make and use" and "best mode" requirements of 35 USC 112 are met, a working example is not mandatory if none actually exists and the invention is otherwise disclosed (in this case in detail) so that one skilled in the art can practise it without undue experimentation. In re Borkowski et al. (CCPA 1970) 422 F2d 904, 164 USPQ 642; In re Gay (CCPA 1962) 309 F2d 769, 135 USPQ 311; In re Stephens et al. (CCPA 1976) 529 F2d 1343, 188 USPQ 649; Ex parte Krenzer (POBA 1978) 199 USPQ 227. Since 35 USC 112 does not demand a "working example", an application cannot be fatally defective merely because it lacks one (in respect of a disease or condition) so long as persons skilled in the art understand and can use the invention. In re Long (CCPA 1966) 368 F2d 892, 151 USPQ 640; In re Honn et al. (CCPA 1966) 364 F2d 454, 150 USPQ 652. In re Bartholome et al. (CCPA 1967) 386 F2d 1019, 156 USPQ 20; Ex parte Kenaga (POBA 1974) 189 USPQ 62. The patent and Trademark Office has the burden of showing that the disclosure entails undue experimentation. In re Angstadt (CCPA 1976) 537 F2d 498, 190 USPQ 214.

Applicants' disclosure of their invention is addressed to persons skilled in the art. You, the Examiner, in light of the above submissions have the burden of showing that the disclosure does not teach how the invention is to be used. You have the burden of establishing there is a requirement for undue experimentation. Applicants respectfully submit this burden has not been overcome. In this regard, the Application is very clear. Furthermore, even

human testing is not always required to establish the utility of a claimed compound or composition whose intended use is include human consumption. See Carter-Wallace Inc., and Riverton Laboratories Inc., (SDNY 1969) 304 FSupp 357, 164 USPQ 73; In re Langer (CCPA1974) 503 F2d 1380, 183 USPQ 288.

While Applicants respectfully submit they have discharged any burden upon them (assuming there is a burden, which is denied), nevertheless, to assist the Examiner and substantiate the effects of Applicants' Application, Applicants enclose further test data to support the patentability of the subject matter in this Application. The Examiner will note that some of this data is incorporated in PCT Application WO93/16733 (International Application No. PCT/CA93/00062) which was filed with PCT and claims priority from a Canadian Application 2,061,566 filed February 20, 1992 and which Canadian Application corresponds in all respects to this U.S. Application. Applicants did not claim priority from the said Canadian Application (but, if required, will do so by filing a certified copy thereof) because of the fact that this Application and the U.S. Application were filed within two days of each other - mainly because of the time required to courier the Application to the U.S. Patent Office from Canada. (Applicants have entered the National Phase in the United States with this PCT Application.) This PCT Application contains substantial additional tests beginning at page 55 to 57 and 60 to 76. Please note, photographs of persons having basal cell carcinoma are referred to and discussed at page 70 to 71, line 15. These additional tests are submitted as further corroboration of the success of Applicants' invention. This reference, WO93/16733, is attached as **Schedule "A"**. Applicants also enclose as **Schedule "B"**, other tests which have been carried out and further substantiate the applicability of Applicants' invention. **Schedule "B"** attaches a number of schedules under Tabs 1-8 and are identified as follows:

Schedule 1 Skin Residue Experiment; Diclofenac Gel

	Schedule 2	Skin Permeation Study
	Schedule 3	Concentrations of Diclofenac in Human Plasma from a Study Comparing Two Topical Formulations - Study Number EPDICL01
	Schedule 4	2-Way Crossover Multiple Dose Bioavailability Study of Hyal Diclofenac Sodium 3% Topical Gel and Geigy (Voltaren®)
	Schedule 5	Novel Topical NSAID Shows Promise as Analgesic
	Schedule 6	A Placebo Controlled Trial of Topically Administered Diclofenac Versus Diclofenac Formulated with Hyaluronic Acid in the Treatment of Pain Associated with Arthritis
*	Schedule 7	A Novel Approach to the Treatment of Superficial Basal Cell Carcinoma
*	Schedule 8	Untitled - Relating to Basal Cell Carcinoma (BCC)

In respect of all the enclosed data particularly, the results in Schedule 8, please note under "Conclusions" (for treatment of basal cell carcinoma):

> "The current study shows that even with as few as eight weeks of therapy, 86% of patients receiving active product exhibited a positive response to treatment and 40% showed what is considered to be indicative of a clinical cure."

In the Claims, while Applicants disagree with the conclusions of the Examiner with respect to the expression "homologues, analogues, derivatives, complexes, and esters", in order to assist the Examiner with respect to the prosecution of this Application, Applicants have deleted the expression therefrom although, persons skilled in the art would understand what is meant

by the said terms. No undue amount of experimentation would be required to determine the compounds falling within the said expression.

Applicants have, in amending the Claims, also taken into consideration the objections of the Examiner at pages 8 and 9 of the Official Action with respect to the terms used in the Claims. Persons skilled in the art would have no difficulty in selecting non-toxic amounts of the form of hyaluronic acid (because there is little toxicity and amounts as would be understood by persons skilled in the art have been taught). The same is true with the amount of NSAIDS. The 2 gram amounts discussed at page 50 of the Application would be applied. The patients would apply topically (several times a day for several weeks - see Example 1, page 53). The other Examples are to the same effect. No one would have difficulties in determining the dosages having regard to the Formulations and Examples. It is also clear having regard to the teachings in the Application and the incorporation of the teachings in the Parent Application from which this Application is a Continuation-In-Part (and which teachings are incorporated herein by reference in their entirety) that delivery and transport are clearly understood.

Applicants therefore respectfully submit that the Examiner not only has test data specified in the Application which supports the Application but also has additional test results which corroborate the teachings of the Application. There can be no doubt that Applicants have taught and disclosed their invention in full, concise and sufficient details as would be understood by persons skilled in the art.

The Examiner will note that a number of the references have now been published such as the PCT Application. If the Examiner requires that the data and test results be supported by an Affidavit/Declaration, Applicants are

prepared to do so. However, it is clear that from even the PCT published application which is an actual application, and which designates the United States, and which the Examiner is advised has entered the national phase in the United States and thus can be referred to under Applications Serial No. 08/290,848, 08/466,778, 08,468,329, and 08,466/775 (which the Examiner may corroborate), there can be no doubt that Applicants have established their treatments as supported, and even if the Examiner had established a prima facie case of her position, which is denied, Applicants respectfully submit that the test data in the Application and additional test data clearly shows that Applicants' Application is not in breach of 35 U.S.C. 112. Persons skilled in the art would understand having regard to the teachings in the application that the treatments could be applied to all the diseases and conditions specified including basal cell carcinoma. Persons skilled in the art would also know others to which the formulation could be applied once they have read Applicants' Application.

The Examiner will note that the Claims as amended are now very specific and have taken into account the objections of the Examiner at pages 9 and 10. Claim 10 consists of the generic names of the drugs not trademarks for the drugs. Claim 9 refers to Claim 8 which depends ultimately from Claim 6 which mentions drug (see middle of Claim 6). The identificaiton of molecular weight is within the knowledge of persons skilled in the art.

With respect to the rejections under 35 U.S.C. 103, it is now clear that the Claims are differentiated from Delle Valle, U.S. Patent No. 4,736,024 and Schultz, U.S. Patent No. 4,808,576. The Examiner questions Applicants' conclusions on the reading of Delle Valle. Applicants submit as follows:

Delle Valle does not teach percentage compositions or the formulations as taught by Applicants, does not teach the methods of treatment as

taught by Applicants, nor the amounts as taught by Applicants. Delle Valle specifies only the use of drops (very, very small amounts less than 1 mg) of Hyaluronic Acid put into the eye of an animal where it sits and provides a retard effect so that the medicine can leach out from the vehicle and pass into the eye. While Applicants have discussed this patent (and Schultz) in the earlier response and adopts the submissions therein, the Examiner is referred to the following places in the patent which clearly teach the use of drops only, column 26, line 27, (one drop), column 27, lines 56-57 (microsyringe 10 mcl), column 30, line 37 (one drop - 50 µl) (50 microlitres (.05 mL)) - very small amounts. The use of the Hyaluronic Acid to vehicle the drug forms a homogeneous stable film on the cornea, column 30, line 66 to 68 from which the pilocarpine teaches. Note that it is only the pilocarpine which penetrates transcorneally, column 30, line 65. The film on the cornea is the Hyaluronic Acid. Please also note column 2, the following general statement about the invention, namely,

> "One advantage of the present invention is having perfected new types of collirium in which the above defects have been overcome. The use of Hyaluronic Acid as a vehicle for opthalmic drugs allows for the formulation of excellent preparations free from concentration gradients of the active substance and, therefore, perfectly homogeneous, transparent and adhesive to the corneal epithelium, without sensitization effects, with excellent vehicling of the active substance and possibly with a retard effect." (column 2, lines 41 to 51).

It is thus clear that there is no penetration or transportation actively caused by the Hyaluronic Acid or a form thereof. In fact, there is a retard effect

and a film which adheres to the corneal epithelium. Della Valle also asserts that the formulations may not only be used opthalmically, but may be used in dermatology and in diseases affecting the mucous membranes. However, the same approach would be the case, the use of drops to sit on the surface of the skin or mucous membranes to provide a retard affect for the Medicine. It is therefore clear that Della Valle did not appreciate Applicants' invention of the treatment of the diseases specified and the manner of such treatment a number of times daily for a prolonged period. Additionally, Della Valle did not appreciate Applicants' formulations in the percentage concentrations taught to achieve those methods of treatment or the dosage amounts which are actually taught in Applicants' application to transport and penetrate so that both the Hyaluronic Acid and medicine go into the skin, into the epidermis where the medicine and Hyaluronic Acid are accumulated -- completely different from Della Valle.

This Della Valle patent reference, no. 4,736,024 is part of a group of worldwide patents and applications filed by Della Valle (and Fidia S.p.A.). One of the other references is European Patent Application No. 0197718. A discussion of the other Fidia references is attached as **Schedule "C"**.

In Applicants' respectful submission, the Claims are neither anticipated nor obvious in light of Delle Valle. This reference does not teach the subject matter of Applicants' Claims (methods, compositions and dosages claimed). Delle Valle does not teach the uses of his invention for the purposes of Applicants' invention. Nor does he even allude, suggest or contemplate anything in that direction. This is clear from Fidia's teachings. The Examiner also relies on Della Valle with the patent to Schultz, U.S. Patent No. 4,808,576.

U.S. Patent No. 4,808,576 relates to the remote administration of hyaluronic acid which is effective according to the inventors in reducing pain

and the swelling of traumatized or irritated mammalian tissue particularly, joint tissue (column 2, line 67 to column 3, line 2). A discussion under "Summary of the Invention" at column 3, between lines 5 and 22 follows:

> "A process for reducing the sequela of the trauma in irritated or inflamed mammalian tissue by the remote administration of hyaluronic acid or a pharmacologically acceptable salt thereof has been discovered. (Hereinfter for convenience the term hyaluronic acid is used to denote both the free acid and the pharmacologically acceptable salts thereof interchangeably except where otherwise explicity indicated.) The hyaluronic acid is introduced to the body of the mammal at other than the site of the traumatized tissue and is effectively transported to the site of action by the body's internal processes. This allows the use of such convenient routes of administration as intramuscular, intravenous, subcutaneous, and topical. Two particularly preferred routes of administration are intramuscular injection and topical applicaiton in a recognized transdermal carrier and a particularly amenable condition for such treatment is irritated or inflated joint tissue."

Thus, according to the invention for the treatment of reducing pain and swelling of traumatized or irritated mammalian tissue particularly, joint tissue, dosage amounts of hyaluronic acid can be given. They can be given intramuscularly, intravenously, subcutaneously, and topically (column 3, line 17-20). The routes utilized are those except for direct application to the effected

tissue, i.e. Applicants' treatment is directly to the basal cell carcinoma lesion. Of prime interest should be the discussion at column 5, between lines 1-36. Various average molecular weights are provided for use. However, those preferred are those in excess of a million. Schultz speculates that those greater than 50,000 would be useful but, nevertheless, insists that for topical application, the higher molecular weights of hyaluronic acid are used (column 5, lines 30-35). Additionally, the higher viscosities are convenient for topical applications while the lower viscosities are convenient for injection routes of administration (column 5, lines 24-30). It is thus clear that Schultz transports nothing, that Schultz is applied topically in high molecular weights. (The Examiner will appreciate that Applicants' preferred molecular weights are those below 750,000 and, where they are too high, they may be autoclaved to reduce their size. The reason, therefore, is to permit transportation as discussed in the Parent Application and this Application as previously discussed which transportation is of the NSAID to the epidermis to do its job. In other words, the invention is based on the discovery that hyaluronic acid acts as a transport agent when used in molecular weights less than 750,000 or where autoclaved to reduce their size, when the higher molecular weights are being used to reduce the size. Schultz does not recognize transport by hyaluronic acid into the skin (to treat basal cell carcinoma, for example); nor does Delle Valle. When combined, they do not teach Applicants' invention as discussed by the Examiner at page 12, lines 3-4. Because Applicants have now omitted "comprising" from the Claims and inserted the expression "consists essentially of" (being a treatment consisting essentially of the administration of the formulations the basal cell carcinoma is cleared), Applicants have now included claim limitations which are not included in Schultz, Delle Valle, or the combination thereof. (Applicants deny they were there in the first place.) The depot effect of Delle Valle discussed in the middle of page 13 of the Action and is referred to the Examiner's attention as being found in the words at column 2, lines 45-51 which provide a retard effect and thus a

depot holding the medicine within the drops and leaching them slowly thereby providing a retard effect would be understood by persons skilled in the art from the teachings. Delle Valle does not teach Applicants' method. Nor does Schultz particularly, when Schultz, for topical application, uses high viscosities and high molecular weights and does not even suggest the use of a medicine therewith. If it did, Schultz would be no more than Delle Valle only submitting the hyaluronic acid for topical application remote from the site in need of treatment letting the body's natural mechanisms or processes take the hyaluronic acid to the area in need of reduction of the pain and swelling of traumatized or irritated mammalian tissue particularly, joint tissue. The high viscosity and high molecular weight means that it sits topically and Applicants question whether or not Schultz could even work at all for topical methods of treatment. The reason is that Schultz requires a transport agent to "get the hyaluronic acid through the skin". Schultz did not appreciate Applicants' invention. Schultz uses DMSO as his transport agent to "get the HA in". Dimethysulfoxide is notoriously known for its transportation characteristics and it would be the carrier for hyaluronic acid into the skin when applied topically as in Examples 2 and 4. (The Examiner will recall the test with DMSO wherein DMSO was rubbed on the skin and, thirty seconds later, the person tastes garlic in his/her mouth. It is clear that Schultz uses a transdermal carrier to "get" the high viscosity, high molecular weight hyaluronic acid into the skin. It is not the hyaluronic acid that enters itself (see the Examples).

It is also clear that Applicants' treatments by its formulations are novel and provide unexpected utility, namely the treatment of basal cell, carcinoma, actinic keratoses, psoriasis, tumours in the skin, etc., and the results of the use of Applicants' invention are totally unexpected. In the treatment of basal cell carcinoma using Applicants' invention, without surgical involvement, the success rate is 86% (see Schedule "8" of Schedule "B"). This invention is not

only not taught by the combination of the references, but additionally, also provides unexpected utility not taught by the references or any other prior art of which Applicants are aware. Applicants have enclosed other references with this Response, **Schedule "E"**, a copy of U.S. Patent No. 3,887,703 and a **Schedule "F"** which is made up of **"A"** to **"H"** which contain a copy of U.S. Patent No. 4,303,676 ("A"), U.S. Patent No. 4,937,254 ("B"), a copy of Canadian Patent Application No. 2,031,880 ("C"), a copy of U.K. Patent Application No. GB2099826 ("D"), a copy of Canadian Letters Patent 1,205,031 ("E"), an article entitled "Drug Delivery Systems using Hyaluronan and its derivatives ("F"), an article entitled "'Natural' Moisturizers for Cosmetics" ("G"), and an article entitled "Polymers and Skin Cosmetics" ("H") to assit the Exmainer. (None teach the treatment of Basal Cell Carcinoma.)

With respect to U.S. Patent No. 3,887,703, we refer the Examiner's attention to Example 14 found at column 1, lines 19 through 30. Please note that the dosage amounts of the formulation given are several drops. Please also note that the percentages of each of Salicylic Acid and Mucopolysacarides relative to the total weight of the composition is less than 1%. Therefore, although a purported pharmaceutical composition may have been prepared, the dosage amounts are drops, and the percentages of the mucopolysacarides and salycilic acids are each less than 1% in the finished formulation.

With respect to the expression "mucopolysacarides", Applicants enclose two articles as "G" and "H" entitled "Natural Moisturizers for Cosmetics" Drug and Cosmetic Industry 1985; 136 (5) (May): 24-26 ("G") and "Polymers In Skin Cosmetics", Cosmetics and Toiletries, 1988; 103: 63-68, ("H"). In both references, Hyaluronic Acid is referred to as a munopolysacaride (MPS). The articles teach that about 70% of all MPS are Hyaluronic Acid. The rest are condroitan sulfates. Because of the use of only several drops taken from the

formulation of Example 14 for use to be massaged into the scalp, such drops would not provide the dosages of Applicants' application nor the methods of treatment. Thus, U.S. Patent No. 3,887,703 is irrelevant.

The said reference is also irrelevant for the purposes of the treatment claims using the concentrations of the forms of hyaluronic acid and medicine and dosages because the percentages of the components are less than 1% (in the order of about .45%).

With respect to U.S. Patent No. 4,937,254, "B" of Schedule "E", Example 19 should be reviewed through to the top of column 23. Compositions are prepared; however only drops are administered. In this regard, see Example 19, column 21 at lines 53 to 55. The double uterine horn adhesion molecule described above in Example 17 was employed. In Example 17 at column 19, line 55 "the sodium salt of Tolmetin were dripped on the traumatized site and the rabbits were then closed". It is therefore clear that only drops were used. Additionally, the drops used include percentage amounts of Sodium Hyaluronate between about .5 to 1.5% and small amounts of the NSAID, .2% - the formulation is for use to inhibit the formation of adhesions. It is therefore clear that the formulation of the said patent is not the same compositions that Applicants have used. Nor does this patent teach the methods of treatment that Applicants have taught nor the dosage amounts suitable for treatment that are claimed. This reference is irrelevant.

With respect to dripping, the traumatized site would have involved a large surface area inside the rabbit from which the dripped-on formulation would run and co-mingle with other fluids of the body. Thus the area to which the dripping was applied would not be a small area, but would include a large area on the inside of the animal. Furthermore, the said formulation taught in

U.S. Patent No. 4,937,254 is not for topical application. The rabbits underwent a lower median laparotomy incision. The formulation was not applied to the skin or normally exposed tissue, but rather to the tissue in the abdomen exposed by the surgical procedure. (Laparotomy is defined as a surgical incision into the abdomen at the flanks or less precisely at any point.) Thereafter the rabbits were closed. This formulation having been dripped onto the tissue exposed by the incision (and free to run away) does not constitute a dosage amount as described by Applicants. Furthermore, the formulation does not comprise a dosage amount, the percentage concentrations set out by Applicants in Applicants' claims, and finally the pharmaceutical composition is not a composition for topical application and is not a multi-gram pharmaceutical composition, for example 50 grams from which dosage amounts can be taken as described by Applicants in their Application.

Canadian Letters Patent 1,205,031 are part of Fidia's Patents filed around the world containing the same teachings as for example, European Patent 0 197 718 which teaches the same formulation and uses as U.S. Patent 4,736,024. The European Patent Application 0 197 718 identifies the same inventors as does this Canadian Patent discloses similar teachings and contains many of the same examples. With respect to pilocarpine nitrate vehicled in hyaluronic acid disclosed at page 25, line 12, the dosage amounts are "drops" (see page 26, line 21) from a micro syringe (10 l) (sic). The same is true with the EGF vehicled in hyaluronic acid (pages 33 and 34). Two drops were administered (see also page 36 for formulations comprising gentamicin).

U.K. Patent Application GB 2 099 826 A relates to compositions for use in cosmetic formulations which includes forms of hyaluronic acid and as preservatives, bacteriostatic and fungistatic substances. No dosage amounts containing forms of hyaluronic acid and medicinal or therapeutic agent are

taught. Furthermore, no pharmaceutical compositions from which the dosage amounts can be taken are taught as well.

U.S. Patent 4,303,676 is to the same effect as U.K. GB 2,099,826 A.

Canadian Patent Application 2,031,880 teaches combinations of sodium hyaluronate and NSAIDS. However, they are for injection purposes and not topical application.

Finally, with respect to the article entitled "Drug Delivery Systems Using Hyaluronan and its Derivatives", please note that the hyaluronan being used (referred to at page 280) has an average molecular weight of $5 - 6 \times 10^6$. Please also note at page 281, that drops are taken from the hyaluron and pilocarpine solution for administration to the eye. At page 282 Hylan gel formulations are discussed for administration to the eye by drops (see page 284 and the description under Figure 3) and wherein the gentamicin was gradually released from the formulation on the corneal surface for absorption. The drops or dosage amounts are 50 microlitres (see page 284). Note also the amount of gentamicin is less than 1%, in fact being .3%.

It is therefore clear from the above art, which Applicants submit is representative of the prior art available, that the claims as proposed by the Applicants are clearly new, useful and inventive. Schultz and Delle Valle together do not teach this combination. The claims for the methods of treatments as presented are not taught by the prior art, either explicitly or implicitly.

As additional support of their position, Applicants refer Examiner Krikorian to the case of In re Laskowski, 10 U.S.P.Q. 2d 1397 in which the Court of Appeals of the Federal Circuit held that

"Although the Commissioner suggest that Hoffman could readily be modify to form the Laskowski structure, "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification". In re Gorden, 733 F2d 900, 902, 221 UAPQ 1125, 1127 (Fed. Cir. 1984), In re Sernaker, 702 F2d 989, 994, 217 USPQ 1, 5 (Fed. Cir. 1983).

The prior does not suggest Laskowski's modification of the Hoffman band saw wheel, or provide any reason or motivation to make that modification. In re Regal, 526 F2d 1399, 1403 n.6, 188 USPQ 136, 139 n.6 (CCPA 1975) ("there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references") (citing In re Stemniski, 44 F2d 581, 170".

In other words Hindsight is 20/20 and that is precisely the Examiners' view point. Having purported to have found "bits and pieces" of Applicants' invention in the prior art, the Examiner has combined the references without motivation. No persons reading the prior art would be motivated to develop Applicants' formulations or any of Applicants' formulations from the prior art teachings.

In order for a combination of references to render an invention obvious, it must be apparent that their teachings can be combined. In re Avery (CCPA 1975) 518 F2d 1228, 186 USPQ 161. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teachings, suggestion or incentive supporting the combination. In re

Geiger (CAFC 1987) 815 F2d 686, 2 PQ2d 1276; In re Fine (CAFC 1988) 837 F2d 1071, 5 PQ2d 1596. When the incentive to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. Ex parte Skinner (BPAI 1986) 2 PQ2d 1788. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination, Berghauser v. Dann. Comr. Pats. (DCDC 1979) 204 USPQ 393; ACS Hospital Systems, Inc. v. Montefiore Hospital (CAFC 1984) 732 F2d 1572, 221 USPQ 929. Citing references which merely indicate that isolated elements and/or features recited in the Claims are known is not a sufficient basis for concluding that the combination of Claimed elements would have been obvious. Ex parte Hiyamizu (BPAI 1988) 10 PQ2d 1393. The same conclusion is true where the references expressly teach away from what the PTO contends is obvious from the references, In re Grasseli et al. (CAFC 1983) 713 F2d 731, 218 USPQ 769, or, where the examiner's proposed modification would render the prior art version unsatisfactory for its intended purpose. Ex parte Rosenfeld (POBA 1961) 130 USPQ 113. Accord, In re Gordon, 733 F2d 980, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); In re Kramer (CAFC 1990 Unpublished decision) 18 PQ2d 1415. The references, viewed by themselves and not in retrospect, must suggest doing what applicants have done. In re Shaffer ()CCPA 1956) 229 F2d 476, 108 USPQ 326, In re Skoll (CCPA 1975) 523 F2d 1392, 187 USPQ 481.

The mere fact it is possible for two isolated disclosures to be combined does not render the result of that combination obvious absent a logical reason of record which justifies the combination. In re Regel et al. (CCPA 1975) 526 F2d 1399, 188 USPQ 136. To properly combine two references to reach a conclusion of obviousness, there must be some teachings, suggestion or inference in either or both of the references, or knowledge generally available to one of ordinary skill in the art, which would have led one to combine the

relevant teachings of the two references. Ashland Oil Inc. v. Delta Resins and Refractories, Inc. et al. (CAFC 1985) 776 F2d 281, 227 USPQ 657; 5 PQ2d 1532. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in Applicants' disclosure. In re Vaeck (CAFC 1991) 20 USPQ F2d 1438.

The mere allegation that the differences between the claimed subject matter and the prior art are obvious does not create a presumption of unpatentability which forces an Applicants to prove conclusively that the Patent Office is wrong. In re Soli (CCPA 1963) 317 F2d 941, 137 USPQ 797. The ultimate legal conclusion of obviousness must be based on facts or records, not on the Examiner's unsupported allegation that a particular structural modification is "well known" and thus obvious. Subjective opinions are of little weight against contrary evidence. In re Wagner et al. (CCPA 1967) 371 F2d 877, 152 USPQ 552. If the examiner seeks to rely upon a theory of chemistry for obviousness, he must provide evidentiary support for the existence and meaning of that theory. In re Grose et al. (CCPA 1979) 592 F2d 1161, 201 USPQ 57. Unless the Applicants question the accuracy of a statement of the Examiner unsupported by the art of record (for example by requesting a Rule 107 affidavit), or by presenting evidence to contradict it, it will probably be accepted as true on appeal. In re Shapleigh (CCPA 1957) 248 F2d 96, 115 USPQ 129; In re Lundberg et al. (CCPA 1957) 244 F2d 543, 113 USPQ 530 MPEP 706.02(a). Data in the specification showing the claimed article possesses characteristics not possessed by the prior art should be accepted as accurate, notwithstanding the contrary opinion expressed sua sponte by the Board of Appeals. In re Ehringer (CCPA 1965) 347 F2d 612, 146 USPQ 31, (shock-resistant, vibration-resistant and non-sag filament wire...).

Finally, Applicants wish to refer the Examiner's attention to the recent decision of the U.S. Court of Appeal's Federal Circuit In re Soni, 34 U.S.P.Q. (2d), 1684, and particularly to page 1686 in the "Discussion" in the case by the majority. A copy of the decision is enclosed as **Schedule "G"**. The issue in that case was whether or not Soni's patent specification showed that the compositions of the Claims exhibited unexpected utility over the prior art. In that case, the Examiner in the Appeal Board chose what to accept and what not to accept, accepting what was good for their decision and conclusions and refusing to accept other statements made by Soni, namely that the improvements were much greater than would have been predicted. In that case, the majority for the Court of Appeal determined that unexpected results to a case of prima facie obviousness is established when a patent applicant demonstrates substantially improved results and states that the results were unexpected in the absence of evidence to the contrary. The majority of the Court held,

> "mere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates substantially improved results as Soni did here, and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary."

The Examiner has taken the position that Applicants' invention is not appropriately taught to support Claims for the processes. Applicants have submitted data in the application and additional test data to refute the statement such that even if a prima facie case had been established by the Examiner (which is denied), same had been refuted. The said formulations, methods of treatment and dosages were not taught in the prior art, and that same provide unexpected utility. Applicants have provided substantial overwhelming corroboration to

the data in the application. Persons skilled in the art would have no trouble treating by the teachings in the Application and preparing dosages for the treatments from the teachings herein.

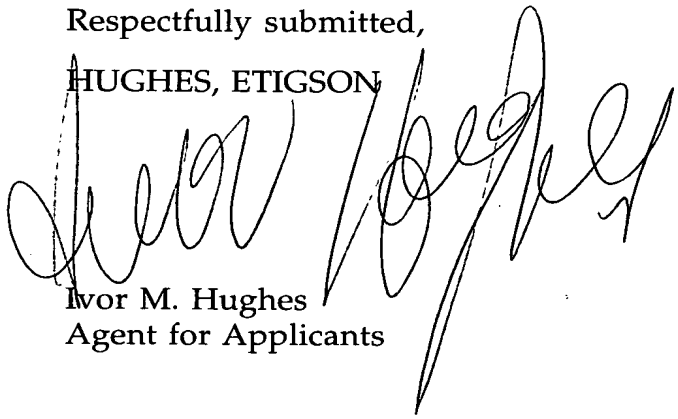
A number of other areas must be dealt with. At paragraph 19 of the Official Action, the Examiner requests several incomplete literature citations be completed. Applicants are unable to provide the literature citations at this point in time but will endeavour to find them. The difficulty was that they were mentioned in some newspapers or publications which are not now readily available.

Additionally, the Examiner, in paragraphs 31, 32, 33, and 34 has provisionally rejected the Application of the Claims herein in view of the Claims of other applications. Applicants wish to advise that the inventions have always been commonly held by the same Assignee which presently is Hyal Pharmaceutical Corporation of all the Applications. Applicants will, when Claims submitted herein have been allowed over the prior art, make submissions to the Examiner why the Claims herein are patentable over and above the Applications cited by the Examiner in the said Clauses 31 to 34 inclusive of the Official Action or file appropriate terminal disclaimers, the suitability of which will be discussed with the Examiner.

After the Examiner has had an oppportunity to review the enclosed, Applicants' Agent will be in touch with her to set up a meeting to discuss the progress and continued examination of this Application and the other Applications discussed in the Official Action and to give the Examiner any further submissions and data which can assist.

In view of the above submissions, Applicants submit that their application is in condition for allowance, and same is solicited at the earliest convenience. If the Examiner has any questions or concerns, she is respectfully requested to contact Ivor Hughes at (905) 771-6414, collect at her convenience.

Respectfully submitted,
HUGHES, ETIGSON



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